

In re of Appln. No. 09/687,122
Response dated November 9, 2004
Reply to Office action of August 9, 2004

against which administration of a TNF receptor is effective by administering a combination of the TNF receptor and DHEA.

Claims 22-24 and 32 have been withdrawn from consideration. However, in view of the indication of allowability of claims 30 and 31, claim 32 should also be rejoined and examined in this case. Claim 30 is clearly generic to the species of both claims 31 and 32. As claim 30 has been indicated to be allowable, then both species should be rejoined and examined in this case.

Claims 21 and 25-29 remain rejected under 35 U.S.C. §112, first paragraph, for lack of enablement commensurate in scope with the claims. The examiner states that the claims encompass the treatment of any and all inflammatory and autoimmune diseases by administration of a TNF receptor in combination with DHEA. The examiner states that while the preamble of the claim in the Jepson format serves as an admission that it is prior art to the instant application, it does not serve as a limitation on the claim, whereby the claim is limited to only what is known in the prior art. The examiner states that the claims encompass methods of treating any and all inflammatory and autoimmune diseases by administration of a TNF receptor in combination with DHEA, and while the specification

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demonstrates the effectiveness of the claimed treatment in a septic shock model and the art teaches the effectiveness of TNF receptor alone in RA, SLE and the NOD mouse model of diabetes, this is not demonstrative of any and all autoimmune and inflammatory conditions, and does not enable one of skill in the art to treat any and all autoimmune and inflammatory conditions using the claimed method. This rejection is respectfully traversed.

Respectfully, the examiner is incorrect in stating that the claims are directed to the treatment of "any and all inflammatory and autoimmune diseases". While the examiner is correct that the preamble of a claim in the Jepson format does not serve to limit the claim to what is known in the prior art, it does limit and further define what autoimmune and inflammatory diseases may be treated under the claim. The words "against which a tumor necrosis factor (TNF) receptor is effective" cannot be read out of the claim as the examiner is apparently doing. The claim is only directed to a method for treating those autoimmune and inflammatory diseases against which TNF receptor is effective in a patient. This language clearly does not read on the treatment of any and all inflammatory and autoimmune diseases.

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The examiner concedes that there is enablement in the specification for the treatment of septic shock, RA, SLE and diabetes. This is a large group of autoimmune and inflammatory diseases. Additionally, attached hereto are the following abstracts:

Bachmaier et al, "Low-molecular-weight tumor necrosis factor receptor p55 controls induction of autoimmune heart disease" *Circulation*, 95:551-2 (1997)

Christadoss et al, "Treatment of experimental autoimmune myasthenia gravis with recombinant tumor necrosis factor receptor Fc protein" *J Neuroimmunol*, 122:186-90 (2002)

Dick et al, "The role of tumour necrosis factor (TNF-alpha) in experimental autoimmune uveoretinitis (EAU)" *Prog Retin Eye Res*, 23:617-37 (2004)

Hunger et al, "Inhibition of submandibular and lacrimal gland infiltration in nonobese diabetic mice by transgenic expression of soluble TNF-receptor p55" *J Clin Invest*, 98:954-61 (1996)

Goluszko et al, "Tumor necrosis factor receptor p55 and p75 deficiency protects mice from developing experimental autoimmune myasthenia gravis" *J Neuroimmunol*, 122:85-93 (2002)

Mukherjee et al, "TNF receptor gene therapy results in suppression of IgG2a anticollagen antibody in collagen induced arthritis" *Ann Rheum Dis*, 62:707-14 (2003)

Su et al, "Reduction of arthritis and pneumonitis in motheaten mice by soluble tumor necrosis factor receptor" *Arthritis Rheum*, 41:139-49 (1998)

Zaccone et al, "Autoimmune thyroid disease induced by thyroglobulin and lipopolysaccharide is inhibited by soluble TNF receptor type I" *Eur J Immunol*, 32:1021-8 (2002)

Thus, in addition to those inflammatory and autoimmune diseases for which the examiner concedes that the art teaches

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the effectiveness of TNF receptor alone in their treatment, i.e., septic shock, RA, SLE and the NOD mouse model of diabetes, Mukherjee teaches the effectiveness of TNF-R for collagen-induced arthritis, Bachmaier discloses effectiveness in controlling induction of autoimmune heart disease, Dick relates to the treatment of autoimmune uveoretinitis, Zaccone relates to the treatment of autoimmune thyroid disease, Christadoss and Goluszko deal with the treatment of experimental autoimmune myasthenia gravis, Su relates to the treatment of arthritis and pneumonitis, and Hunger states in the last sentence of the abstract that the results of that paper "indicate beneficial effects of soluble TNF receptors in the treatment of organ-specific autoimmune diseases."

This large number of inflammatory and autoimmune diseases, against which it is known that a tumor necrosis factor receptor is effective, should be sufficient to establish enablement for the entire genus. Only a representative number of species in a genus need be established in order to be able to claim the genus. As stated in the last section of MPEP 2164.02:

For a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art (in view of the level of skill, state of the art and the information in the specification) would expect the claimed genus could be used

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in that manner without undue experimentation. Proof of enablement will be required for other members of the claimed genus only where adequate reasons are advanced by the examiner to establish that a person skilled in the art could not use the genus as a whole without undue experimentation.

Here, the examiner's comments and citation of references about autoimmune and inflammatory diseases in general are not applicable to the wording of the present claims, which are limited to the treatment of those autoimmune and inflammatory diseases against which a TNF receptor is effective. If a TNF receptor is effective against the autoimmune or inflammatory disease, then one of ordinary skill in the art reading the present specification would expect that effectiveness would be improved by the combined treatment with DHEA. The examiner states that there is no nexus between the treatment of RA, SLE and the NOD mouse model of diabetes or septic shock. However, those of ordinary skill in the art should understand that the nexus is the effect of TNF on the initiation and continuation of such conditions. TNF, and specifically TNF- α , is the linking nexus. The TNF receptor is known to inhibit the binding of TNF- α to its receptor. Thus, any autoimmune or inflammatory disease that involves the adverse effects of TNF- α would be expected to be one against which a TNF receptor is

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effective, as is well known in the prior art. Accordingly,
the present claims are not broader than enablement.

If TNF-R is not effective against the disease, then
the present claims do not encompass it. If TNF-R is effective
against the disease, then it would be expected that DHEA would
improve that effectiveness. The fact that there may be some
autoimmune diseases about which it is not yet known whether
TNF-R is effective should not prevent applicant from getting
the coverage specified. The claims are certainly no broader
than what would be expected to be operable. Reconsideration
and withdrawal of this rejection is therefore respectfully
urged.

It is submitted that all of the claims now present
in the case clearly define over the references of record and
fully comply with 35 U.S.C. §112. Reconsideration and
allowance are therefore earnestly solicited.

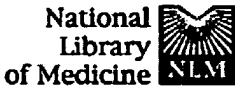


Respectfully submitted,

BROWDY AND NEIMARK, P.L.L.C.
Attorneys for Applicant(s)

By


Roger L. Browdy
Registration No. 25,618

RLB:jab
Telephone No.: (202) 628-5197
Facsimile No.: (202) 737-3528
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Low-molecular-weight tumor necrosis factor receptor p55 controls induction of autoimmune heart disease.

Bachmaier K, Pummerer C, Kozieradzki I, Pfeffer K, Mak TW, Neu N, Penninger JM.

Amgen Institute, Ontario Cancer Institute, Canada.

BACKGROUND: Tumor necrosis factor-alpha (TNF-alpha) is involved in the pathogenesis of myocarditis and can bind to either tumor necrosis factor receptor (TNF-R) p55 or TNF-Rp75. However, it is not known which TNF-R mediates the specific functions of TNF in disease. To determine the role of the TNF/TNF-R system in chronic heart disease, we used a murine model of cardiac myosin-induced myocarditis that closely resembles the chronic stages of virus-induced myocarditis in humans. **METHODS AND RESULTS:** Mice lacking TNF-Rp55 expression after targeted disruption of the TNF-Rp55 gene were backcrossed into a genetic background susceptible to the induction of myocarditis with cardiac myosin. Here, we demonstrate that TNF-Rp55 gene-deficient mice did not develop any inflammatory infiltration into the heart after autoantigen injection, whereas control littermates showed autoimmune myocarditis at high prevalence and severity. Despite the absence of autoimmune heart disease, TNF-Rp55^{-/-} mice produced cardiac myosin-specific IgG autoantibodies, indicating that activation of autoaggressive T and B lymphocytes had occurred. However, heart interstitial cells failed to express major histocompatibility complex (MHC) class II molecules in TNF-Rp55^{-/-} animals, and adoptive transfer of autoreactive T cells resulted in heart disease only in TNF-Rp55^{-/-} but not in TNF-Rp55^{-/-} littermates. **CONCLUSIONS:** Cardiac myosin-induced myocarditis is dependent on autoaggressive T cells and on autoantigen presentation in association with MHC class II molecules within the heart. Thus, lack of TNF-Rp55 expression could interfere with either lymphocyte activation or target organ susceptibility. The data presented here show that the TNF-Rp55 is a key regulator for the induction of autoimmune heart disease by its controlling target organ susceptibility.

PMID: 9024154 [PubMed - indexed for MEDLINE]

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ELSEVIER SCIENCE
FULL-TEXT ARTICLE

Treatment of experimental autoimmune myasthenia gravis with recombinant human tumor necrosis factor receptor Fc protein.

Christadoss P, Goluszko E.

Department of Microbiology and Immunology, University of Texas Medical Branch,
301 University Boulevard, 3.142 MRB, Galveston, TX 77555-1070, USA.
pchrista@utmb.edu

Lymphotoxin-alpha (TNF-beta) and TNF receptor p55 gene knockout mice are resistant to the development of antibody and complement mediated experimental autoimmune myasthenia gravis (EAMG), suggesting a possible role of TNF in mediating EAMG. Therefore, we tested the hypothesis that blocking the functional interaction of TNF with their receptors by soluble recombinant human TNFR:Fc would suppress the ongoing clinical EAMG. Recombinant human TNFR:Fc administered daily for 2 weeks to C57BL6 mice with ongoing clinical EAMG significantly improved clinical EAMG when compared with placebo-treated mice. A clinical trial of selected myasthenia gravis patients with recombinant human TNFR:Fc could be attempted.

PMID: 11777558 [PubMed - indexed for MEDLINE]

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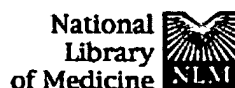
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☐ 1: Prog Retin Eye Res. 2004 Nov;23(6):617-37.[Related Articles, Links](#)**ELSEVIER SCIENCE
FULL-TEXT ARTICLE**

The role of tumour necrosis factor (TNF-alpha) in experimental autoimmune uveoretinitis (EAU).

Dick AD, Forrester JV, Liversidge J, Cope AP.

Department of Clinical Sciences at South Bristol, University of Bristol, Bristol Eye Hospital, Lower Maudlin Street, Bristol BS1 2LX, UK.

The pleiotropic cytokine tumour necrosis factor-alpha (TNF-alpha) is released from cells that include macrophages and T-cells during inflammatory responses, orchestrating the initiation of further leucocytic infiltration via adhesion molecule upregulation, dendritic cell maturation and survival, macrophage activation and driving Th1 T-cells responses within tissues. Exposure to TNF also plays a role in maintaining tissue homeostasis, particularly relating to resident cell responses of both microglia and retinal pigment epithelium. Depending on the balance between duration and dose of TNF exposure, an environment where full expression of inflammatory and autoimmune responses within tissues may occur. In experimental autoimmune uveoretinitis (EAU), increased tissue concentrations of TNF facilitate the on-going T-cell effector responses and macrophage activation. These are responsible for targeted and bystander tissue damage and can be suppressed by anti-TNF therapies, in particular, those directed at the p55 TNF receptor. The ability to suppress disease experimentally has led to the successful translation of anti-TNF therapy for treatment of uveitis in cohort studies and phase I/II trials where, additionally, altered peripheral blood CD4(+) T-cell profiles can be demonstrated following each treatment.

PMID: 15388077 [PubMed - in process]

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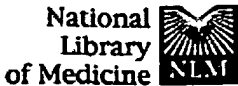




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ELSEVIER SCIENCE
FULL-TEXT ARTICLE

Tumor necrosis factor receptor p55 and p75 deficiency protects mice from developing experimental autoimmune myasthenia gravis.

Goluszko E, Deng C, Poussin MA, Christadoss P.

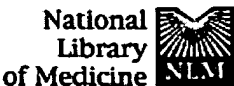


Department of Microbiology and Immunology, University of Texas Medical Branch, 301 University Boulevard, 3.142 MRB, Galveston, TX 77555-1070, USA.

The precise pathogenic role of proinflammatory cytokines belonging to the tumor necrosis factor (TNF) family has not been investigated yet in antibody-mediated myasthenia gravis (MG) and experimental autoimmune myasthenia gravis (EAMG). In this study we report that TNF receptor p55(-/-) p75(-/-) mice were resistant to the development of clinical EAMG induced by acetylcholine receptor (AChR) immunizations. The resistance was associated with reduced serum levels of IgG, IgG(1), IgG(2a), and IgG(2b) anti-AChR antibody isotypes. However, IgM anti-AChR antibodies were not reduced, suggesting defective anti-AChR IgG class switching in TNF receptor p55(-/-) p75(-/-) mice. We thus demonstrate the genetic evidence for the role of TNF receptor p55 and p75 in EAMG pathogenesis, and their requirement for the generation of anti-AChR IgG antibodies.

PMID: 11777546 [PubMed - indexed for MEDLINE]

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Inhibition of submandibular and lacrimal gland infiltration in nonobese diabetic mice by transgenic expression of soluble TNF-receptor p55.

Hunger RE, Muller S, Laissue JA, Hess MW, Carnaud C, Garcia I, Mueller C.

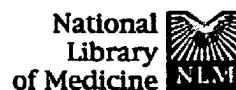
Department of Pathology, University of Bern, Switzerland.

Besides a prominent mononuclear cell infiltration of the islets of Langerhans, nonobese diabetic (NOD) mice also show massive cellular infiltrates of the submandibular and lacrimal glands concomitant with histological signs of tissue damage. To obtain insights into the mechanisms operative during the initiation and progression of tissue damage, we followed by in situ hybridization the appearance of cells containing mRNA of the gene encoding the proinflammatory cytokine TNF-alpha in the cellular infiltrates. Cells expressing TNF-alpha are mainly located in infiltrates, are absent in nonaffected glands, and are preferentially found among CD4 T cells. Secretion of TNF-alpha by gland-infiltrating cells was confirmed by an ELISPOT procedure. Direct evidence for an instrumental role of TNF-alpha in initiation and progression of submandibular and lacrimal gland infiltration is provided by the observed significant reduction in the extent of infiltration in nonobese diabetic mice transgenic for a soluble TNF receptor p55 fused to the Fc part of human IgG3. This protection from infiltration is paralleled by decreased expression of the adhesion molecules ICAM-1 and VCAM-1 in submandibular and lacrimal glands. These data suggest a central role of TNF-alpha in the initiation and progression of autoimmune tissue destruction of salivary glands and indicate beneficial effects of soluble TNF receptors in the treatment of organ-specific autoimmune diseases.

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www.annrheumdis.com**TNF receptor gene therapy results in suppression of IgG2a anticollagen antibody in collagen induced arthritis.****Mukherjee P, Wu B, Mayton L, Kim SH, Robbins PD, Wooley PH.**

Department of Immunology and Microbiology, Wayne State University School of Medicine Detroit, MI 48201, USA.

BACKGROUND: Therapeutic strategies to block tumour necrosis factor alpha (TNFalpha) activity in experimental autoimmune arthritis models and rheumatoid arthritis (RA) have proved highly successful, and provide sustained beneficial effects. **OBJECTIVE:** To examine whether TNFalpha inhibition has immunological activity beyond the reduction of inflammation in collagen induced arthritis (CIA), an established experimental model of RA. **METHODS:** Arthritic DBA/1 mice received single periarticular injections of retroviral constructs encoding human TNF receptor (TNF-R) into the affected arthritic paw, at the onset of arthritis. Severity of arthritis, antibodies to collagen type II (CII), and extent of pathological joint damage of arthritic paws were compared between TNF-R and media treated (control) animals 3, 7, 14, 21, and 49 days after disease onset. **RESULTS:** Severity of CIA was significantly decreased in TNF-R treated animals compared with controls, 14-34 days after disease onset. Joint destruction was reduced in TNF-R injected joints and in the uninjected contralateral and ipsilateral paws of TNF-R treated animals. Seven days after disease onset, TNF-R treated mice had lower levels of inflammatory Th1 driven IgG2a antibodies to CII ($p < 0.05$) than controls. This altered the anticollagen IgG2a:IgG1 ratio towards Th2 driven IgG1. **CONCLUSIONS:** Local TNF-R gene therapy in CIA appears to have systemic effects on the anti-CII antibodies. The overall influence of TNF-R gene therapy is that it inhibits the progression of CIA mainly by suppressing the inflammatory Th1 response rather than by stimulating a Th2 response. Therefore, periarticular TNF-R gene therapy may have excellent therapeutic potential in RA.

PMID: 12860724 [PubMed - indexed for MEDLINE]

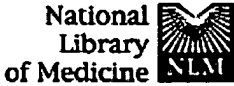


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Reduction of arthritis and pneumonitis in motheaten mice by soluble tumor necrosis factor receptor.

Su X, Zhou T, Yang P, Edwards CK 3rd, Mountz JD.

The University of Alabama at Birmingham, 35294-0007, USA.

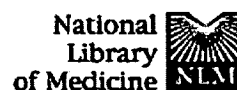
OBJECTIVE. To determine the effects of anti-tumor necrosis factor (anti-TNF) therapy in the inflammatory and autoimmune disease in motheaten (me/me) mice, which exhibit a Fas apoptosis signaling defect. **METHODS.** Arthritis, pneumonitis, and mortality were analyzed in me/me mice treated with a novel, soluble, dimeric TNF receptor I (sTNFRI) molecule capable of high-affinity binding and neutralization of TNFalpha. **RESULTS.** Soluble TNFRI reduced serum levels of TNFalpha and led to a 2-fold increase in the lifespan of me/me mice, compared with the control treatment group. The treatment also reduced the development of the "motheaten" skin patches and alleviated pneumonitis and inflammatory lesions in the extremities of me/me mice compared with controls. However, the serum levels of IgM and IgM anti-double-stranded DNA autoantibody were comparable to those of untreated control mice. **CONCLUSION.** TNFalpha is an important cytokine involved in the pathogenesis of inflammatory disease in me/me mice, resulting in tissue damage and early mortality. Therapies directed at blocking TNF/TNFR interactions, such as the sTNFRI used in these experiments, may be effective in diseases associated with apoptosis defects leading to overutilization of the TNF/TNFR pathway.

PMID: 9433879 [PubMed - indexed for MEDLINE]

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Fig. 1. Motheaten mice.



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Autoimmune thyroid disease induced by thyroglobulin and lipopolysaccharide is inhibited by soluble TNF receptor type I.

Zacccone P, Fehervari Z, Blanchard L, Nicoletti F, Edwards CK 3rd, Cooke A.

Department of Pathology, Immunology Division, Cambridge University, Cambridge, GB.

Experimental autoimmune thyroiditis (EAT) is inducible in mice by immunization with thyroglobulin and adjuvant. Previous studies have shown that EAT is an autoimmune Th1-mediated disease but its characteristics differ with the adjuvant. Granulomatous lesions with marked follicular disruption develop following administration of thyroglobulin (Tg) and complete Freund's adjuvant (CFA) whereas when lipopolysaccharide (LPS) is used as the adjuvant only focal infiltrates of mononuclear cells are observed. The pro-inflammatory cytokine, TNF-alpha, is associated with Th1 autoimmune-mediated conditions. Cytokine antagonists have been used as potential therapeutic agents in several experimental autoimmune models. Soluble cytokine receptors belong to this category and may naturally be shed from cell membranes to inhibit cytokine activity. We show that the administration of the soluble TNF receptor type I (sTNFR I) in the induction of EAT has very different effects on the two models of induced autoimmune thyroiditis. sTNFR I treatment inhibits the induction of EAT only when mouse Tg is given with LPS not with CFA, suggesting an important difference in the pathogenic processes.

PMID: 11920568 [PubMed - indexed for MEDLINE]

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